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ASSESSMENT OF TOXICITY

A Memorandum prepared by the Toxicology Committee* of the
Medical Research Council

One of the functions of the Medical Research Council is to advise Government Departments on questions involving the use of the latest knowledge in medical science. In answering such questions, the Council are guided by a number of expert advisory Committees, of which their Toxicology Committee is one. The role of the Toxicology Committee in this field is to discover and interpret the available information about the safety or harmfulness of chemical compounds to which the general population or a particular group of it may be exposed, and to make suggestions for further research work where this is deemed to be necessary. Such tasks as those of defining the conditions of safe use or the setting of permitted concentrations in foods or other consumer goods depend so largely on factors outside the purview of the Committee that the Committee cannot in general undertake the formulation of practical advice. Nevertheless it is possible to outline some of the considerations which may govern the conditions of use of toxic materials. This memorandum sets out some of these principles in order to assist the work of applying appropriately the scientific knowledge available.

DATA FROM TOXICITY TESTS

There is no prescribed pattern of toxicity tests to be applied routinely to every compound studied from the point of view of its toxic properties. The Committee believe that the precise nature of the tests to be applied after the preliminary results of the examination of any compound become available must be determined by the investigator's knowledge and experience.

In general all toxicity data should include the following information:

(*a*) The size of the single lethal dose when administered by mouth either undiluted or in a suitable solvent such as water, vegetable oil or other assimilable vehicle. An approximation to the LD50 should be given together with the range between the smallest dose having any toxic effect and that which kills the animals. As variation in species sensitivity may be considerable tests should be done on, say, rats or mice, rabbits or guinea pigs, dogs or cats and in special cases monkeys might be included.

(*b*) The objective signs of poisoning elicited by a dose not immediately fatal with a note on their duration. The outstanding naked eye and microscopic lesions in the animals that die.

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(*c*) The cumulative effect of repeated doses below the level of a single toxic dose. Occasionally, as with the insecticides chlordane and aldrin for example, small daily doses may kill an animal before the total quantity administered amounts to a single lethal dose.

(*d*) The maximum concentration in the diet of rats or other species that may be consumed during the period of their most rapid growth without impairing this growth or affecting their general condition.

(*e*) An opinion as to the general mode of action of the compound if it has a well marked toxic effect, supported by the necessary experimental evidence.

(*f*) Evidence of the metabolic fate of the material after its ingestion. Thus the artificial sweetening agent—cyclo hexyl sulphonate—is largely excreted unchanged. The pyrethrins are rapidly broken down in the mammalian stomach whereas DDT is partly metabolised and partly stored in the body fat. In some cases it may be the metabolic products that are responsible for the toxic action of a compound. Species may differ in the ways in which they metabolise a compound.

(*g*) Special tests for skin penetration or toxicity by inhalation where the chemical properties or proposed uses indicate the need for such tests. Thus inhalation of vapour is the usual way in which poisoning by methyl bromide takes place. In the case of nicotine both the vapour and liquid concentrates may be dangerous as the latter rapidly penetrate the skin. Other less toxic materials such as chlordane may be dangerous as concentrates in organic solvents which can rapidly penetrate the skin when splashed on. The diluted suspensions on the other hand are much less dangerous.

The value of many of the tests carried out in an attempt to prove the absence of a toxic effect (e.g. under 1 (*d*)) may be open to doubt on purely scientific and statistical grounds. However, they form the only reasonable type of administrative safeguard that can at present be recommended. A specific sensitive test such as the reduction of cholinesterase activity is very valuable but the existence of such specific indicators of toxic action is exceptional.

THE "SAFETY FACTOR"

Even with relatively extensive toxicity tests on animals it is impossible to create in the laboratory conditions corresponding to the exposure of thousands or millions of the human race to a potentially toxic compound. Only occasionally do the data from animal experiments lend themselves to extrapolation in terms of the doses likely to be ingested by human populations. More rarely still are there any data on the sensitivity of man to repeated small doses of the materials under consideration. It is therefore necessary to assume that man has a sensitivity to any chemical at least as great as that of the most sensitive animal; and further to decide on a level for human exposure, considerably below the threshold dose in the most sensitive animal, which could be regarded as providing an adequate margin of safety for humans and which may be expressed by the term "safety factor".

The magnitude of this safety factor must depend on the seriousness of the toxic reaction when it occurs. In general a factor of 100 has come to be accepted as generally reasonable. The possibility of unpredictable reactions in man and the enormous size of the population at risk means that such a factor may not be excessive. In the usual type of feeding test on animals the substance being examined is added in a known proportion to the whole diet, often expressed as so many parts per million by weight (ppm). The daily food consumption of a rat is about 10 per cent. of its body weight, i.e. at least ten times that of an adult human, and on the same basis the water intake of a rat is about three times that of a man. This provides another safety factor in extrapolating from animal experiments, but it does not apply in the case of infants who consume relatively much more in relation to their weight.

MINIMIZING EXPOSURE

In general the exposure of the human population to any chemical should be kept as small as possible, and as far as possible encouragement should be given to the use of less toxic materials where alternatives exist. Where the amount of a given compound to be added to food or administered in some other way is still below the permitted level arrived at by the extrapolation described above, an additional safeguard is obtained by setting the limits only as high as are required in practice. Economic considerations such as the cost of a pesticide may limit to some extent the quantity that is applied. Anomalous situations may arise when substances of different practical efficiency are compared. Thus a pair of insecticides may be equally toxic to mammals but unequally toxic to insects under conditions of use so that an effective level for one is greater than that for the other. If the calculated safe level of both compounds were equal that of the more efficient one might be set at a lower level than that of the less efficient one to meet the principle set out as above.

SPECIAL CONSIDERATIONS

i. **Chemicals present in food or drink**

(a) *Staple Foods.*—In general foreign chemicals believed to possess any toxic activity whatever should not be permitted in staple foods such as cereal products, meat and potatoes. These form the greater part of the diet normally consumed throughout their lifetime by the whole population. Milk, as the sole food of many babies, must also be free from added chemicals.

(b) *Special Foods.*—Foods which may form a substantial part of the diet of invalids and infants such as fruit juices, purees, etc., require special scrutiny.

(c) *Localisation of Toxic Material.*—Toxic material may be concentrated on the outer surface, e.g. the peel of fruit and vegetables or the rind of cheese. It would not be reasonable to assume that in every instance food will only be consumed after thorough cleansing and removal of the outer parts. The total content of the toxicant in the food should be considered in setting limits, except perhaps in the case of potatoes where the residue is on the peel.

When a pesticide is applied to the exterior of a non-living substance such as cheese, diffusion would presumably be governed by simple physicochemical considerations. On the other hand, when a stable material is applied to the outside of living tissues (growing fruit, for example), the final distribution might not be so easy to predict.

(d) *Metabolic Fate.*—Where studies on the toxicology of a compound reveal that it is rapidly metabolised and broken down into harmless by-products, this may be taken as an additional safety factor when considering permitted levels. However, reliance should not be placed on speed of metabolism as a major safety factor, since individuals may by unusual constitution or through disease lack the metabolic pathway normally present. Substances about which little or nothing is known of their fate after ingestion must be treated more carefully whenever exposure to them is likely to be continuous or prolonged over many years.

Although tolerance to some toxic compounds, e.g. nicotine, is readily developed, this possibility should never be taken into consideration in setting limits.

(e) *Chemical Determinations.*—Safe limits cannot be laid down unless methods exist for making a reliable and accurate estimate of the quantities present at the level of the permitted limit.

In general attempts to lay down permitted limits should not be made until there are data available on the quantities that may be expected to be present under conditions of proper use. Until such data are available such possibilities as loss by decomposition, volatilisation and during processing cannot properly be taken into account.

ii. **Occupational exposure**

(a) *Route of Absorption.*—Information on toxicity by inhalation and skin absorption should be available where risk of exposure by these routes is present. Where the exposure is to air-borne droplets the size distribution of the particles should be known. If the particles are above 7-10 microns few if any will be carried to the lungs but will be held in the upper respiratory tract and finally swallowed. On the other hand these larger droplets may comprise a far greater mass of the inhaled material and if direct absorption takes place through the mucosa of the upper respiratory tract this may be as dangerous as inhalation into the lungs.

(b) *Safety Factor.*—This may be smaller where exposure is taking place among small groups over whom some degree of general or medical surveillance will be maintained.

(c) *Precautions.*—These should be the minimum considered necessary for safety. Where elaborate precautions are necessary for safety, recommendations for proper supervision must be included. Continued medical observations may enable changes to be recommended in the light of continued experience. Where the use of masks and respirators is recommended the type must be specified. The ability of protective garments such as gloves and boots to resist penetration of the toxic material must be established.

CONCLUSION

Animal experiments alone can never prove whether or not a material is "safe"; however, in present circumstances the permissible degree of exposure for man must depend upon an intelligent appraisal of the results of experiments on animals, taking account of such factors as have been enumerated above.

Further, the extent to which the population may be exposed to risk as a result of a proposed use of a toxic substance must also depend on such an appraisal, made as precisely as possible.

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